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RESEARCH ARTICLE

Distinct cerebral small vessel disease impairment in early- and late-onset Alzheimer's disease

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Abstract

Objective: This study investigated cerebral small vessel disease (CSVD) damage patterns in early-onset and late-onset Alzheimer's disease (EOAD and LOAD) and their effects on cognitive function. **Methods**: This study included 93 participants, 45 AD patients (14 EOAD and 31 LOAD), and 48 normal controls (13 YNC and 35 ONC) from the ADNI database. All participants had diffusion tensor imaging data; some had amyloid PET and plasma p-tau$_{181}$ data. The study used peak width of skeletonized mean diffusivity (PSMD) to measure CSVD severity and compared PSMD between patients and age-matched controls. The effect of age on the relationship between PSMD and cognition was also examined. The study also repeated the analysis in amyloid-positive AD patients and amyloid-negative controls in another independent database (31 EOAD and 38 LOAD), and the merged database. **Results**: EOAD and LOAD showed similar cognitive function and disease severity. PSMD was validated as a reliable correlate of cognitive function. In the ADNI database, PSMD was significantly higher for LOAD and showed a tendency to increase for EOAD; in the independent and merged databases, PSMD was significantly higher for both LOAD and EOAD. The impact of PSMD on cognitive function was notably greater in the younger group (YNC and EOAD) than in the older group (ONC and LOAD), as supported by the ADNI and merged databases. **Interpretation**: EOAD has less CSVD burden than LOAD, but has a greater impact on cognition. Proactive cerebrovascular prevention strategies may have potential clinical value for younger older adults with cognitive decline.

Introduction

Alzheimer's disease is divided into early-onset (EOAD) and late-onset (LOAD) based on an age cutoff of 65 years, with EOAD accounting for approximately 4–6% of AD cases.[1] The two subtypes differ not only in age but also in clinical presentation, with EOAD often exhibiting worse attention, executive function, and visuospatial ability compared to LOAD.[2] These clinical features could result in misdiagnosis, an average delay in diagnosis of about 1.6 years, and shorter survival than LOAD.[3–5] White matter involvement in EOAD is greater in posterior cingulate and parietal regions and major anterior–posterior pathways than in LOAD, with less involvement in mesial temporal tracts.[6] Although both subtypes share the same AD pathological hallmarks, EOAD has a more widespread distribution of amyloid plaques and neurofibrillary tangles, particularly in the frontoparietal cortex.[7,8]

Numerous studies have shown that AD pathology and cerebral small vessel disease (CSVD) frequently coexist.[9,10] Post-mortem studies have indicated that AD patients generally have higher cerebral vascular pathology degrees than normally aging healthy individuals.[11] With the development of imaging techniques, it has become well-established that CSVD contributes to cognitive decline and modifies the progression to AD.[12–14] However, it

remains unclear whether EOAD and LOAD exhibit different CSVD damage patterns and whether CSVD has distinct cognitive impacts on these two dementia subtypes. In vivo, limitations in detecting small vessels of the brain hinder such explorations. Conventionally, we have evaluated CSVD through parenchymal alterations visible on MRI, leading to the identification of four main MRI features as CSVD markers, including white matter hyperintensities (WMHs), enlarged perivascular spaces (ePVS), microbleeds (MBs), and lacunes.[15] However, these conventional CSVD markers have limitations and may not have sufficient sensitivity for detecting mild vascular damage. For instance, previous studies have reported alterations in white matter microstructural integrity in regions that appear normal on MRI in AD patients.

Recent studies have proposed a robust and fully automated imaging marker for CSVD called the peak width of skeletonized mean diffusivity (PSMD). The skeletal map of mean diffusion (MD) eliminates cerebrospinal fluid contamination, and the histogram-based approach enhances the ability to capture subtle diffuse disease features.[16] PSMD has been applied in patients with CSVD, AD, and the normal aging population, demonstrating its potential as a more reliable CSVD marker than conventional markers.[16–18] In addition, PSMD is superior to other conventional CSVD measures in associations with clinical symptoms and predicting cognitive performance.[19,20]

This study aimed to compare the CSVD between EOAD and LOAD subtypes based on PSMD, and analyze the effects of CSVD on cognition in young-and-old groups. We hypothesized that both EOAD and LOAD subtypes have a more severe burden of CSVD compared to their respective controls and that CSVD has a more significant impact on cognitive function in EOAD than in LOAD.

Materials and Methods

Participants

Participants in this study underwent MRI and neuropsychological evaluations, as well as amyloid PET and p-tau$_{181}$ plasma assessments for some. General cognitive ability and dementia severity were measured using the Mental State Examination (MMSE) and Clinical Dementia Rating Scale Sum of Boxes (CDR-SB). Cognitive function was assessed in different domains using composite scores (UW-Neuropsych Summary Scores) for memory and executive functions, and clock-drawing test (CDT) and semantic verbal fluency (SVF) for visuospatial and language functions, respectively.

Neurologists made diagnosis of AD from multiple sites based on the ADNI research protocol. AD patients were categorized into early-onset (<65 years) and late-onset (≥65 years) groups and healthy older adults were divided into young (YNC) and older (ONC) groups based on age, with YNC and ONC groups matched to the corresponding patient groups in terms of age, education, and sex.[4,8]

We defined YNC and ONC as individuals with a CDR score of 0, an MMSE score between 24 and 30 (inclusive), a score of 9 or more on the Wechsler Memory Scale logical memory (WMS-LM) delayed recall test with at least 16 years of education, a score of 5 or more on the WMS-LM delayed recall test with 8–15 years of education, or a score of 3 or more on the WMS-LM delayed recall test with seven or fewer years of education, and no clinical depression (Geriatric Depression Scale score <6) or dementia. Participants with significant neurological, psychiatric, and medical disorders, a history of severe traumatic brain injury, non-AD-related medications that may affect brain function and drug or alcohol abuse were excluded. Ultimately, we identified 14 EOAD, 31 LOAD, 13 YNC, and 35 ONC. Another independent dataset from the Zhejiang University (ZJU dataset) included 31 EOAD, 38 LOAD, 22 YNCs, and 22 ONCs (Supplementary Material 1).

MRI acquisition

Each participant underwent a 3 T MRI scanner. Specific acquisition information includes: (1) The T1-weighted structural imaging sequence used an IRSPGR protocol with parameters TR = 6.96 ms, TE = 2.8 ms, TI = 400 ms, FOV = 256 × 256, voxel size = 1.02 mm × 1.02 mm × 1.2 mm, and a flip angle of 11°. (2) DWI data were acquired using an echo planar imaging sequence with 41 directions, 59 sections, an acquisition matrix of 256 × 256, and a voxel size of 1.4 mm × 1.4 mm × 2.7 mm. The protocol included 41 dispersion-weighted images (b = 1000 s/mm2) and five non-dispersion-weighted images (b = 0 s/mm^2) with a flip angle of 90°. The TR varied from 12,500 ms to 13,000 ms across 14 ADNI sites. (3) Axial T2*-weighted MRI scans were acquired using a gradient echo sequence with parameters TR = 650 ms, TE = 20 ms, Flip angle = 20°, and 50 slices with a slice thickness of 4.0 mm. (4) T2 FLAIR scans were acquired using an echo-planar imaging sequence with parameters TR = 9000 ms, TE = 90 ms, and TI = 2500 ms. MRI acquisition details for the ZJU dataset can be found in Supplementary Material 1.

Amyloid PET

We downloaded the UC BERKELEY-AV45 file using predefined regions of interest (ROI), including frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal regions. Standardized uptake value ratios (SUVRs) were calculated using the whole cerebellar as the

reference region [21]. Of note, 11 out of 13 YNC, 12 out of 14 EOAD, 33 out of 35 ONC, and 28 out of 31 LOAD had amyloid SUVR data available, and participants were classified as either amyloid-positive or amyloid-negative based on a previously reported composite amyloid SUVR cutoff of 1.11.[21,22] We identified 10 A- YNC, 11 A+ EOAD, 25 A- ONC, and 26 A+ LOAD (Supplementary Material 2). Amyloid PET data were not available for participants in the ZJU dataset.

Plasma p-tau$_{181}$

We obtained plasma p-tau$_{181}$ data from the ADNI using the single-molecule array (Simoa) technique developed in Gothenburg, Sweden.[23,24] 11 of 13 YNC, 12 of 14 EOAD, 33 of 35 ONC, and 27 of 31 LOAD had p-tau$_{181}$ data available. The ZJU dataset did not have plasma p-tau$_{181}$ data.

Image processing and analysis

Peak width of skeletonized mean diffusivity analysis

Diffusion-weighted image preprocessing was done with the eddy correct software from 'FDT,' FMRIB's Diffusion Toolbox (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT).[25] The PSMD is a fully automatically computed imaging marker publicly available (http://psmd-marker.com). Processes include tensor fitting, skeletonizing the DTI data, applying a custom mask, and computing a histogram analysis.[16] The computation is divided into three main steps: (1) white matter tract skeletonization using tract-based statistics (TBSS) and the FMRIB 1 mm fractional anisotropy (FA) template thresholded at an FA value of 0.2 (tract-based spatial statistics: voxel-wise analysis of multi-subject diffusion data). Mean diffusivity (MD) images were projected onto the skeleton employing the FA-derived projection parameters. To avoid contamination of the skeleton through CSF partial volume effects, MD skeletons were masked with a standard skeleton thresholded at an FA value of 0.3. (2) excluding CSF-prone regions employing a custom mask. Brain structures adjacent to the ventricles, such as the fornix, were removed. (3) creating a histogram based on the MD values of voxels within the skeleton. The PSMD measure refers to the difference between the 5th and 95th percentiles of the histogram distribution.

To investigate whether there was a regional susceptibility of PSMD in EOAD and LOAD, additional analyses for regional PSMDs were evaluated.[17] Lobar atlas in the Mayo Clinic Adult Lifespan Template (MCALT) extracts regional PSMDs (frontal, temporal, parietal, and occipital, https://www.nitrc.org/projects/mcalt/, Fig. 1, flowchart).[26] Considering the potential impact of different diffusion directions on the PSMD values, we separately analyzed the PSMD data from ADNI and ZJU. Also, after the z-transformation of the PSMD of the two independent

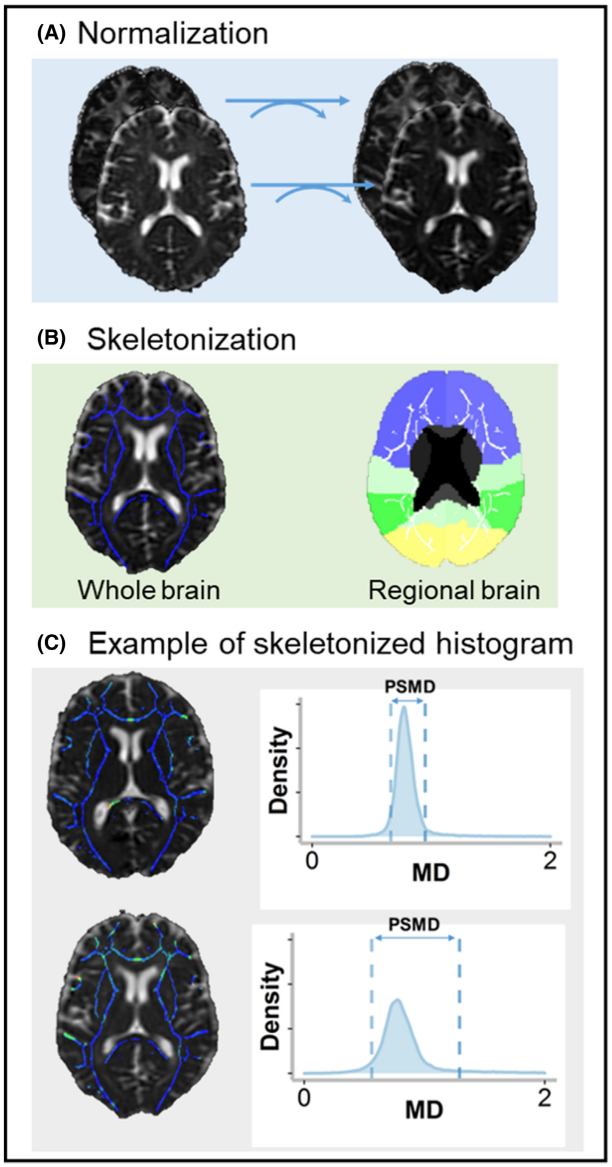

Figure 1. Peak width of skeletonized mean diffusivity (PSMD) calculation involves skeletonization and histogram analysis. Individual fractional anisotropy (FA) images were normalized to standard space (A) and projected onto a skeleton template (B). The transformation and skeleton projection parameters were then applied to mean diffusivity (MD) images. Examples of MD maps from normal control and Alzheimer's disease patient (top and bottom) are projected onto the standard skeleton. PSMD was calculated as the difference between the 95th and 5th percentiles (C). The PSMD of AD patients was found to be higher than that of the control group.

databases separately, the combined analysis results can be found in Supplementary Material 3.

Conventional CSVD markers evaluation

Two blinded experienced neuroradiologists rated the severity of CSVD using T1-weighted structural data to assess enlarged perivascular spaces (ePVS), defined as hypointense signal lesions on T1 of round, ovoid, or linear shape with a maximum diameter <3 mm, having smooth delineated contours.[27] Lacune was defined as CSF-like hypointensity with a surrounding rim of hyperintensities in T2 FLAIR, between 3 and 15 mm. MBs were defined as areas of signal void on T2*-weighted MRI. The number of lacune and MBs was recorded. The CSVD total score, a composite score ranging from 0 to 4 reflecting the overall severity of CSVD, was also evaluated.[28]

WMH volume calculation

FLAIR images were used to segment WMH lesions using an automatic segmentation tool called Lesion Segmentation Tool based on SPM 12.[29] The automatically created WMH label images were then manually corrected to remove falsely classified scalp and tissue as WMH and WMH classified as normal white matter. WMH volumes were extracted and log-transformed due to their positively skewed distribution. This analysis was only performed in the ADNI dataset because FLAIR data were unavailable in the ZJU database.

Hippocampus (HV) and total intracranial volume (TIV)

HV data were obtained from ADNI using FreeSurfer (Version 6.0) to segment MRI scans, with quality checks performed to ensure accuracy. The HV was averaged across hemispheres. Brain volume was calculated and used as a correction index for HV, and WMH volume TIV was calculated using CAT 12 based on T1-weighted images (https://neuro-jena.github.io/cat/). Despite the residual method being shown to provide a greater reduction in physiological between-subject variability compared to the proportional method, we used the proportional method for brain volume correction due to the complexity of the participants in this study (patients and controls, multicenter, two databases).[30] TIV-corrected HV (tHV) and TIV-corrected log-transformed WMH (lgtWMH) were used in subsequent analyses.

Statistical analysis

Statistical analysis was performed using SPSS (Version 26). Raw MMSE scores were converted to zMMSE scores adjusted for age, sex, and education. ANOVA was used to analyze continuous data, including cognition, PSMD, conventional CSVD markers, amyloid SUVR, plasma p-tau $_{181}$, and tHV, followed by post hoc t-tests between AD patients and controls ($p < 0.05$). Categorical sex and vascular risk factors were analyzed using chi-square independent tests. To validate the PSMD results, we compared amyloid-positive AD patients with negative amyloid controls. We also repeated the analysis in the independent ZJU dataset and combined data from ADNI and ZJU to increase the sample size.

Explore the factors contributing to PSMD

To compare the strength of the cognition correlations between PSMD and conventional CSVD markers, we first constructed a partial correlation analysis to correct for the effects of age, sex, and education. We also conducted linear regression with PSMD as the dependent variable, and independent variables included age, sex, education, conventional CSVD markers (lgtWMH, ePVS-BG, ePVS-CC, number of lacunes and MBs), amyloid SUVR, plasma p-tau$_{181,}$ and tHV. The analysis was performed separately in young and old groups to explore age-related differences in the mechanism of PSMD abnormalities. We checked for multicollinearity in the linear model (Supplementary Material 4).

Explore the age effects on the relationship between PSMD and cognitions

In this exploratory study, we aimed to investigate the differences in the impact of PSMD on cognition between young (consisting of YNC + EOAD) and older groups (consisting of ONC + LOAD). A stepwise linear regression model was used with cognition as the dependent variable and age, sex, education, PSMD, amyloid SUVR, plasma p-tau181, and tHV as independent variables. We also analyzed the effect of lobar PSMD on cognitive function. Multicollinearity was analyzed for the linear model (Supplementary Material 4). We used the PROCESS macro to explore the impact of age on the association between PSMD and cognition. We included age, sex, education, amyloid SUVR, plasma p-tau$_{181}$, and tHV as covariates, with PSMD as the independent variable and age group (young versus old) as the moderator variable.

We repeated the same analyses in three more datasets: a group consisting of A+ AD patients and A- controls (Supplementary Material 2), the ZJU database (Supplementary Material 1), and a merged database consisting of ADNI and ZJU data (Supplementary Material 3).

Results

Demographics

Sex and education were not significantly different among YNC, EOAD, ONC, and LOAD in both ADNI and ZJU databases. Additionally, there were no significant differences in cognition (zMMSE) and disease severity (CDR-SB) between EOAD and YNC, as well as LOAD and ONC. Notably, AD patients from the ADNI dataset generally had milder disease severity, better cognition, and higher education than those in the ZJU dataset. Similar results were obtained in the biologically defined participants from ADNI (see Supplementary Material 2). Demographic details of the ZJU and the merged database data of ADNI+ZJU can be seen in Supplementary Materials 1 and 3.

AD pathologies

We observed that amyloid PET SUVR and plasma P-tau$_{181}$ levels increased in EOAD and LOAD groups, respectively, without significant differences between EOAD and LOAD (Table 1). The LOAD group showed smaller tHV than ONC, while no significant tHV difference existed between EOAD and YNC. These findings remained unchanged in the biologically defined participants from ADNI (Table S2). The ZJU and merged databases lacked data on amyloid PET and p-tau$_{181}$. Furthermore, tHV was significantly decreased in EOAD and LOAD compared to their counterparts in the ZJU and merged databases (refer to Tables S1 and S3).

Conventional CSVD

According to ANOVA analysis, significant intergroup differences were observed only in lgtWMH and ePVS-BG. However, post-hoc t-tests indicated no difference in lgtWMH between EOAD and YNC, while LOAD had more lgtWMH than ONC. No significant difference in ePVS-BG was found between EOAD and LOAD and their respective control groups. The four groups did not differ significantly in lacune, MBs, ePVS-CC, and total CSVD scores (Table 2). In the biologically defined participants from ADNI, most results remained unchanged, except that EOAD and LOAD had more lgtWMH than their respective controls (Table S2). Only ADNI data were analyzed for FLAIR data due to their absence in the ZJU database.

Table 1. Epidemiological, cognitive assessment, and AD pathologies in patients and controls.

Demographics	YNC n = 13	EOAD n = 14	ONC n = 35	LOAD n = 31	$F/\chi 2$	p-value
Age, year	63.2 (1.5)	61.8 (2.4)	74.5 (4.4)	76.4 (5.6)	56.6	<0.001
Education, year	17.3 (2.1)	16.0 (2.5)	16.2 (3.7)	15.5 (3.1)	1.0	0.387
Female/male	6/7	10/4	22/13	11/20	7.3	0.062
VRF, No. (%)	5 (11.4)	10 (83.3)	11 (33.3)	18 (66.7)	11.8	0.008[ab]
Smoking						
Hypertension	4 (30.8)	4 (28.6)	3 (8.6)	9 (29.0)	5.6	0.134
Hypercholesterolemia	5 (38.5)	3 (21.4)	19 (54.3)	16 (51.6)	5.1	0.168
Diabetes	5 (38.5)	8 (57.1)	17 (48.6)	15 (48.4)	0.9	0.815
CDR-SB	3 (23.1)	2 (14.3)	3 (8.6)	5 (16.1)	1.9	0.601
Cognition	0.0 (0.1)	4.1 (1.9)	0.1 (0.2)	4.6 (1.6)	107.5	<0.001[ab]
MMSE	29.1 (0.8)	24.4 (4.2)	29.2 (1.0)	23.2 (1.9)	58.9	<0.001[ab]
Memory sum	1.4 (0.6)	−0.2 (0.9)	1.0 (0.4)	−0.9 (0.5)	69.9	<0.001[ab]
Executive sum	1.0 (1.0)	−0.4 (1.1)	0.7 (0.7)	−0.8 (0.9)	20.5	<0.001[ab]
CDT	4.7 (0.5)	3.9 (1.5)	4.7 (0.6)	3.7 (1.3)	6.6	<0.001[ab]
SVF	19.4 (5.7)	16.3 (6.6)	20.4 (4.8)	12.2 (5.0)	14.3	<0.001[b]
NPI-Q	0.3 (0.5)	2.8 (4.2)	0.5 (1.0)	4.1 (3.7)	10.5	<0.001[b]
AD pathologies						<0.001[ab]
Amyloid SUVR	1.1 (0.2)	1.4 (0.2)	1.1 (0.1)	1.4 (0.2)	21.3	<0.001[ab]
p-tau$_{181}$ (pg/mL)	12.3 (4.8)	22.6 (4.9)	12.6 (5.2)	22.9 (11.0)	12.7	<0.001[ab]
tHV	2.8 (0.2)	2.6 (0.5)	2.6 (0.3)	2.0 (0.3)	33.4	<0.001[ab]

The a and b represent the significant difference between YNC and EOAD as well as ONC and LOAD ($p < 0.05$), respectively.
CDR-SB, clinical dementia rating sum score of box; CDT, clock drawing test; EOAD, early-onset Alzheimer's disease; GDS, Geriatric Depression Scale; LOAD, late-onset Alzheimer's disease; MMSE, mini-mental state examination; NPI-Q, Neuropsychiatric Inventory Questionnaire; ONC, old normal controls; SUVR, standardized uptake value ratio; SVF, semantic verbal fluency; tHV, hippocampus volume corrected by total intracranial volume; YNC, young normal controls.

Table 2. Lobar PSMD and conventional CSVD markers in AD patients and controls.

	YNC	EOAD	ONC	LOAD	*F*/χ2	*p*-value
PSMD	2.5 (0.3)	2.7 (0.4)	3.0 (0.6)	3.6 (0.7)	15.3	<0.001[b]
Frontal PSMD	2.1 (0.4)	2.4 (0.5)	2.7 (0.6)	3.2 (0.7)	13.8	<0.001[b]
Parietal PSMD	2.4 (0.2)	2.7 (0.6)	2.9 (0.5)	3.7 (1.0)	14.4	<0.001[b]
Occipital PSMD	2.6 (0.7)	2.9 (1.4)	2.9 (0.6)	3.5 (0.8)	3.8	0.012[b]
Temporal PSMD	2.5 (0.3)	2.5 (0.5)	2.6 (0.4)	3.2 (0.6)	10.1	<0.001[b]
PSMD[1]	2.5 (0.3)	2.8 (4.2)	3.0 (0.4)	3.7 (0.7)	15.2	<0.001[b]
Frontal PSMD[1]	2.2 (0.4)	2.4 (0.5)	2.7 (0.5)	3.3 (0.7)	11.4	<0.001[b]
Parietal PSMD[1]	2.3 (0.3)	2.8 (0.6)	2.8 (0.5)	3.8 (1.0)	13.2	<0001[ab]
Occipital PSMD[1]	2.5 (0.5)	3.1 (1.5)	2.9 (0.6)	3.6 (0.9)	4.3	0.008[b]
Temporal PSMD[1]	2.5 (0.3)	2.6 (0.5)	2.6 (0.4)	3.2 (0.7)	8.2	<0.001[b]
PSMD ZJU	2.6 (0.3)	3.0 (0.4)	3.0 (0.4)	3.4 (0.6)	32.7	<0.001[ab]
Frontal PSMD	2.2 (0.2)	2.6 (0.6)	2.6 (0.3)	2.9 (0.6)	21.8	<0.001[ab]
Parietal PSMD	2.6 (0.4)	3.2 (0.8)	3.2 (0.7)	3.6 (0.9)	25.2	<0.001[ab]
Occipital PSMD	2.9 (0.5)	3.6 (1.0)	3.5 (0.6)	4.0 (0.9)	16.3	<0.001[ab]
Temporal PSMD	2.6 (0.3)	2.8 (0.4)	2.9 (0.4)	3.2 (0.6)	21.6	<0.001[ab]
Conventional CSVD						
lgtWMH	0.1 (0.6)	0.3 (0.6)	0.5 (0.4)	0.8 (0.5)	7.9	<0001[b]
ePVS-BG	2.1 (0.6)	2.2 (0.6)	2.4 (0.6)	2.7 (0.7)	3.0	0.036
ePVS-CC	2.0 (0.6)	2.1 (0.5)	2.2 (0.6)	2.5 (0.7)	2.0	0.122
Lacune (*n*)	0.1 (0.3)	0.1 (0.3)	0.3 (0.8)	0.1 (0.3)	1.0	0.392
MBs (*n*)	0 (0)	0.1 (0.3)	0.1 (0.3)	0 (0)	1.3	0.291
CSVD total score	0.3 (0.6)	0.6 (0.7)	0.8 (0.9)	1.0 (0.8)	2.4	0.069
TIV	1443.6 (117.3)	1376.7 (131.5)	1415.4 (115.1)	1438.2 (163.7)	0.8	0.496

The a and b represent the significant difference between YNC and EOAD, as well as ONC and LOAD ($p < 0.05$), respectively.

CSVD, cerebral small vessel disease; EOAD, early-onset Alzheimer's disease; ePVS-CC and ePVS-BG, enlarged perivascular spaces in the centrum semiovale and basal ganglia; lgtWMH, log-transformed white matter hyperintensities corrected by TIV; LOAD, late-onset Alzheimer's disease; MBs, microbleeds; ONC, old normal controls; PSMD, peak width of skeletonized mean diffusivity; TIV, total intracranial volume; YNC, young normal controls.

[1] PSMD represents analyses only in amyloid-positive AD patients and amyloid-negative controls. PSMD ZJU represents analyses in the ZJU database.

PSMD

LOAD had higher PSMD values than ONC, but no significant difference was observed between EOAD and YNC. The results were largely similar in the biologically defined participants from ADNI, except for a trend towards increased PSMD in EOAD compared to YNC ($p = 0.07$, see Supplementary Material 2). In the ZJU dataset, EOAD and LOAD had significantly higher PSMD values than their respective controls (YNC and ONC). This was also observed in the merged dataset, where EOAD and LOAD had significantly higher PSMD values than YNC and ONC ($p < 0.05$). Table 2, Figure 2, and Supplementary Material 1 provide additional details.

Regarding the lobar level, LOAD had higher PSMD than ONC in all lobes, while no significant difference in PSMD was observed in any lobe between EOAD and YNC. Most of the results for biologically defined participants from ADNI remained unchanged, except for EOAD having significantly increased parietal PSMD compared to YNC ($p = 0.05$). In the ZJU database, EOAD and LOAD had higher PSMD in all lobes than YNC and ONC (Table 2). In the merged dataset, EOAD and LOAD had significantly higher PSMD than YNC and ONC in all lobes ($p < 0.05$, Table S3).

Correlations between PSMD, AD pathologies, and cognition

We found significant differences only in PSMD and lgtWMH among the CSVD markers between AD patients and controls. Therefore, we conducted partial correlation analyses to compare the correlations of PSMD and lgtWMH with cognition. We found that both PSMD and

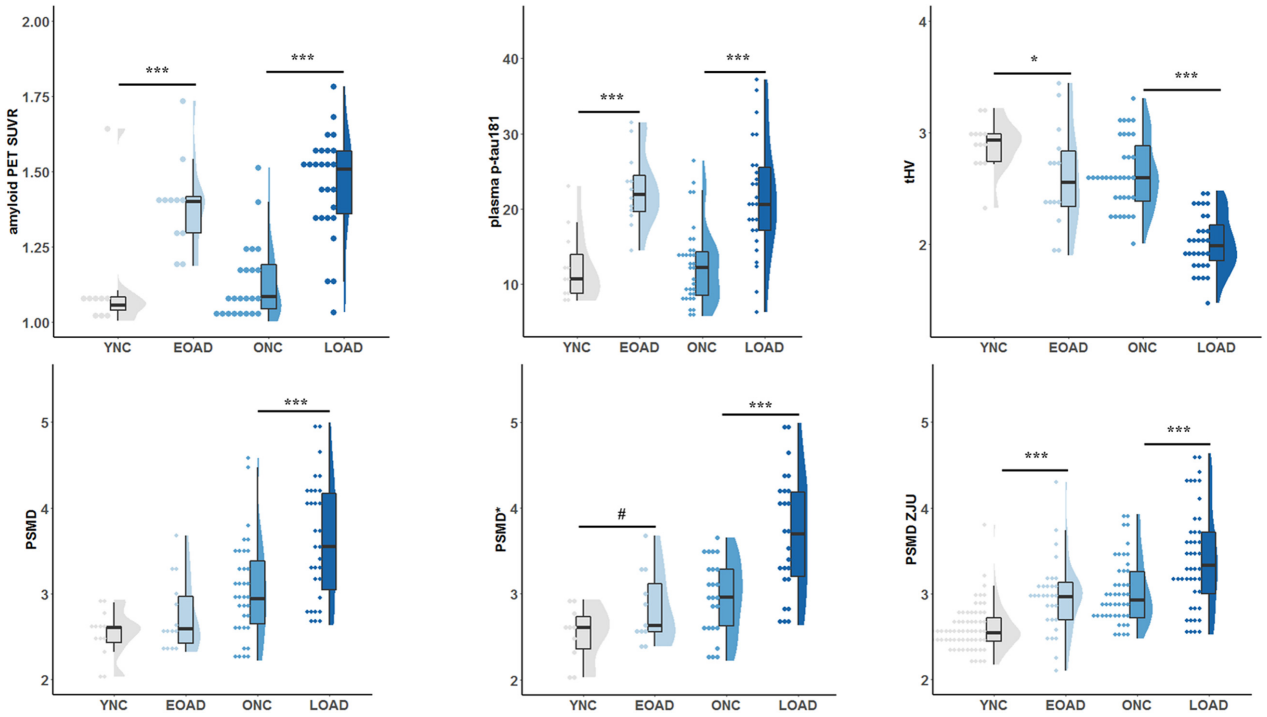

Figure 2. Displays the PSMD values for YNC, EOAD, ONC, and LOAD. Group comparisons were conducted between EOAD and LOAD and their respective controls, with statistical significance denoted by *$p < 0.05$, **$p < 0.01$, **$p < 0.001$. The # symbol represents an increasing trend of PSMD (EOAD > YNC, $p = 0.07$). **PSMD*** and **PSMD ZJU** refer to the subgroup analysis based on the biological definition of AD and the ZJU database, respectively. EOAD, early-onset Alzheimer's disease; LOAD, late-onset Alzheimer's disease; PSMD, peak width of skeletonized mean diffusivity; YNC and ONC, young and old normal controls.

lgtWMH were significantly correlated with zMMSE ($r = -0.43$ and -0.37, respectively, $p < 0.001$) and CDR-SB ($r = 0.39$ and 0.32, respectively, $p < 0.001$) in all participants. PSMD had better clinical relevance than lgtWMH in most cognitive domains, except for visuospatial function (Supplementary Material 5).

Explore the contributing factors of PSMD

We conducted linear regression to explore the mechanisms underlying the increase in PSMD. The results revealed that, in all participants, PSMD was attributed to lgtWMH ($\beta = 0.42$), tHV ($\beta = -0.24$), and ePVS-BG ($\beta = 0.20$). In the young groups (YNC and EOAD), WMH burden ($\beta = 0.56$) was the only factor contributing to PSMD. In the old groups (ONC and LOAD), WMH burden ($\beta = 0.49$), amyloid SUVR ($\beta = 0.24$), and PVS-BG ($\beta = 0.22$) contributed to PSMD (see Supplementary Material 6 for details).

Relationship between PSMD and cognitions

Based on a linear regression model, we found that in the younger groups (YNC and EOAD), PSMD ($\beta = -0.35$), tHV ($\beta = 0.43$), and plasma p-tau$_{181}$ ($\beta = -0.35$) were independent predictors of zMMSE. In the older group, tHV ($\beta = 0.37$) and amyloid SUVR ($\beta = -0.43$) were found to be independent predictors of zMMSE. Moreover, when we divided PSMD by lobe, we found that in the younger groups, tHV ($\beta = 0.50$), frontal PSMD ($\beta = -0.36$), and plasma p-tau$_{181}$ ($\beta = -0.36$) were independent predictors of zMMSE. In the older groups, amyloid SUVR ($\beta = -0.47$) and temporal PSMD ($\beta = -0.40$) were found to be independent predictors of zMMSE.

Based on PROCESS macro, we further investigated the role of young-versus-old in the relationship between PSMD and cognitions. Our main results were: (1) In the ADNI database, for both the whole participants and pathologically defined participants, we found significant moderating effects of age group (young-versus-old) on the relationship between PSMD and MMSE ($p = 0.02$ and 0.04, respectively). (2) In the ZJU database, we did not find significant moderating effects of age on the relationship between PSMD and MMSE ($p = 0.14$). (3) After merging the databases, we discovered significant moderating effects of age on the correlation between PSMD and MMSE ($p < 0.005$), as illustrated in Figure 3.

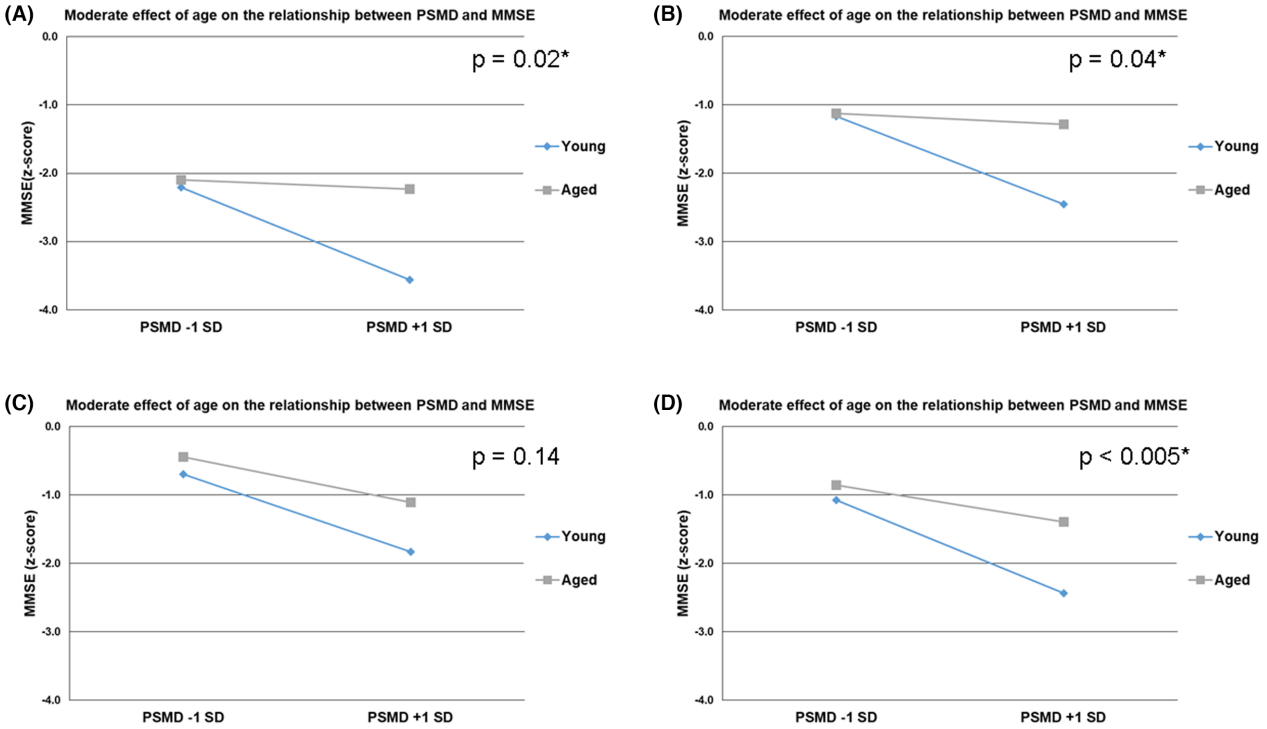

Figure 3. Moderating effect of age on the relationship between peak width of skeletonized mean diffusivity (PSMD) and cognitions. In the ADNI database, for both the whole participants (A) and pathologically defined participants (B), we found significant moderating effects of age group (young-versus-old) on the relationship between PSMD and Mini-Mental State Examination (MMSE) (p = 0.02 and 0.04, respectively). In the ZJU database (C), we did not find significant moderating effects of age on the relationship between PSMD and MMSE (p = 0.14). In the merged database (D), we found significant moderating effects of age on the relationship between PSMD and MMSE (p < 0.005).

The relationship between PSMD and cognitive function at the lobar level could be further viewed in Supplementary Material 7. The results of the multicollinearity analysis suggested that the variance inflation factor (VIF) would be greater than 5 when placing multiple brain lobe PSMDs into the same linear model (Supplementary Material 4).

Discussion

This study examined the impact of cerebral small vessel disease (CSVD) damage patterns on cognitive function in early-onset and late-onset Alzheimer's disease (EOAD and LOAD). The study found that PSMD was associated with cognitive function. In the ADNI database, LOAD had a significantly higher PSMD value, and EOAD tended increased PSMD. EOAD and LOAD had significantly higher PSMD values in ZJU and combined databases. The study also found that PSMD had a greater cognitive impact on the younger group (YNC and EOAD) than the older group (ONC and LOAD). The findings of this study imply that implementing preventative cerebrovascular strategies for cognitive decline in younger elderly populations holds promise for clinical benefit.

We found that PSMD, CSVD total score, WMH, and ePVS-BG were correlated with cognitive function, with PSMD showing the strongest correlation in most cognitive domains except visuospatial function. These results were in line with previous studies that have demonstrated weak associations between conventional CSVD markers and cognitive impairment.[17,19,20] CSVD can cause brain tissue damage beyond what can be detected by visual analysis alone. DTI can measure microstructural integrity that is not visible in conventional clinical scans, which may explain the more substantial clinical relevance of PSMD compared to conventional CSVD markers (except visuospatial function).[16] Although the total CSVD score can provide a complete estimate of the full CSVD impact on the brain, our sample showed a weak correlation between CSVD total score and cognition, consistent with previous studies that found weak associations between conventional CSVD markers and cognitive impairment.[28] This could be attributed to the high frequency of negative findings for markers such as MBs and lacunes and the limited size of our study.

The study found that LOAD had higher PSMD than ONC, while EOAD only showed a trend toward increased

PSMD compared to YNC. In the biologically diagnosed AD subgroup, EOAD showed a trend of increased PSMD. In ZJU and the merged database, LOAD and EOAD had higher PSMD than their counterparts, consistent with previous studies showing more severe CSVD in AD patients than controls.[10,16,31] CSVD is a common age-related phenomenon aggravated by vascular risk factors like hypertension and hyperlipidemia[32]; Thus, the more pronounced CSVD severity in LOAD compared to EOAD could be partially attributed to this. We hypothesized that CSVD might not be severe in early EOAD stages but worsen as the disease progresses. The ZJU database results supported our hypothesis, with EOAD patients having higher PSMD than YNC and worse general cognition than ADNI patients (measured by MMSE: 20.6 ± 3.6 vs. 24.4 ± 4.2). However, DTI acquisition parameter differences may affect PSMD results, and further validation is required through larger longitudinal studies.[33]

We found that in older groups (ONC and LOAD), increased PSMD was due to WMH, ePVS-BG, and amyloid SUVR, while in the younger group (YNC and EOAD), only WMH contributed to PSMD. The contribution of amyloid burden to increased PSMD in older groups may be due to Wallerian degeneration secondary to AD pathologies on the cortex.[34] In addition, PSMD may also indicate the presence of cerebral amyloid angiopathy (CAA), a common age-related CSVD characterized by the accumulation of Aβ in the walls of cortical arterioles and leptomeningeal vessels.[35,36] PSMD is strongly correlated with cognitive function compared to WMH. Therefore, the factors that contribute to an increase in PSMD may include WMH and "invisible CSVD," such as CAA.[16,19] Therefore, it is inferred that the contributing factors to PSMD increase may be WMH and some "invisible CSVD." However, future studies need to test these hypotheses using higher-resolution neuroimaging techniques.

We investigated how CSVD impacts cognition and found that it played a significant role in the cognitive profile of EOAD patients, despite their less severe CSVD than LOAD patients—specifically, in younger groups, PSMD, hippocampal volume, and p-tau$_{181}$ independently contributed to cognition. In comparison, in older groups, hippocampal volume and amyloid SUVR contributed to cognition, with no effect of PSMD. These findings were validated in pathologically defined subgroups. Therefore, we hypothesized that CSVD in EOAD might be more likely an independent risk factor for cognitive impairment rather than a secondary change related to AD pathology. Taking a step further, it can be inferred that CSVD is typically milder in younger individuals but may result in more severe cognitive impairment if it develops at a younger age.

Conversely, our study found that in older individuals (ONC and LOAD), hippocampus volume, amyloid SUVR had a greater impact on global cognition than PSMD, supporting the AD biological research framework, which suggests that amyloid accumulation leads to neurodegenerative changes and gradual cognitive decline.[37] CSVD-related histological lesions are thought to be caused by various mechanisms, such as blood–brain barrier dysfunction or impaired glymphatic clearance.[38–40] In older individuals, increased CSVD is likely a secondary effect of AD pathology, and the effects of CSVD on cognition may be overridden by AD pathology.[41,42] Although we found that PSMD contributed to cognition in both younger and older groups in the ZJU database, which lacked amyloid PET and p-tau$_{181}$ data, this result should be interpreted with caution.

Our study revealed that in EOAD patients, frontal PSMD contributed to global cognition, memory, and language function, while occipital PSMD contributed to visuospatial function. This suggests that CSVD may disrupt intracerebral connectivity, leading to cognitive impairment. A previous study also showed a correlation between WMH burden and executive decline via the frontal–parietal-subcortical circuit.[43] Damage to the posterior white matter may significantly contribute to visuospatial dysfunction in CSVD patients.[44] Our results suggest that CSVD may play a role in the extensive cognitive impairment mechanism of EOAD, highlighting the importance of vascular protection strategies in younger AD patients and normal aging. Temporal PSMD was associated with overall cognition in LOAD patients, possibly due to atrophy and AD pathology in the temporal lobe.[8,45] This is consistent with previous studies suggesting that increased PSMD in older people could be a secondary consequence.[41,42] However, due to multicollinearity issues, caution should be exercised when interpreting these results.

Our study has some limitations. Firstly, the small sample size of EOAD patients is a significant limitation, as the ADNI project was not designed for EOAD research. Although more EOAD patients are in the ZJU database, the lack of AD pathology measurements limits the statistical power. Second, this study did not strictly screen participants using the ATN AD research framework, but we performed subgroup analyses of A + AD patients and A- controls (Supplementary Material 2). The main reason is that plasma p-tau$_{181}$ lacks validated large sample-based cutoff values yet, and the current N+ assessment criteria do not apply to EOAD patients because the EOAD brain atrophy pattern differs from LOAD.[46] Additionally, although we included all four significant MRI-based CSVD markers, some could not be evaluated due to image quality limitations, such as microinfarcts. Lastly,

our study was cross-sectional in design, and further validation in a longitudinal database is necessary.

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Author Contributions

Conception and design: Xiao Luo and Hui Hong. Data analysis: Kaicheng Li, Qingze Zeng, Shuyue Wang, and Yeerfan Jiaerken. Interpretation of results: Zheyu Li, Yanv Fu, Xiaocao Liu, Luwei Hong, Jixuan Li, Xinyi Zhang, and Siyan Zhong. Writing—original draft: Xiao Luo and Hui Hong. Writing—review & editing: Minming Zhang, Peiyu Huang, Yanxing Chen, and Zhirong Liu.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval and Consent to Participate

The Institutional Review Boards approved the ADNI project of all participating institutions, and all participants provided written informed consent. The study was also approved by the Medical Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine. In addition, all participants in the ZJU database provided informed consent.

Consent for Publication

All participants provided written informed consent for their anonymous information to be used for health-related research purposes and publication of the results.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary Material 1.

